DETAILED ACTION

Response to Amendment

Claims 39-42 have been amended, and claims 46 and 47 have been added as requested in the amendment filed on 05 March 2010. Following the amendment, claims 17, 18, 20, 22-25, 36, 37 and 39-47 are pending in the instant application.

Claims 17, 18, 20, 22-25, 36, 37 and 39-47 are under examination in the instant office action.

Objections/Rejections Withdrawn

Applicant's arguments, see pp.1-2 of the Remarks filed 15 October 2009, with respect to the rejection of claims 17, 36, 37 and 45 under 35 U.S.C. 101 for lack of utility have been fully considered and are persuasive. The rejection has been withdrawn.

Applicant's arguments, see pp.1-2 of the Remarks filed 15 October 2009, with respect to the rejection of claims 17, 36, 37 and 45 under 35 U.S.C. 112, first paragraph for lack of utility have been fully considered and are persuasive. The rejection has been withdrawn.

New and remaining issues are set forth below.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims

are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 17, 18, 20, 22-25, 36, 37 and 39-47 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of copending Application No. 11/472,864. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '864 application are drawn to TNF-α variant proteins with amino acid substitutions encompassed by the instant claims. Therefore, the instant claims and those of the '864 application are considered obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 17, 18, 20, 22-25, 36, 37 and 39-47 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4 and 6-11 of copending Application No. 11/559,379. Although the conflicting claims are not identical, they are not patentably distinct from each other

because the claims of the '379 application are drawn to compositions comprising TNF-α variant monomers and homotrimers with amino acid substitutions encompassed by the instant claims. Thus, the instant claims and those of the '379 application are considered obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In the reply filed on 15 October 2009, applicants request that the examiner hold these obviousness-type double patenting rejections in abeyance until there is an indication of otherwise allowable subject matter.

Until such a time occurs, the provisional rejections are maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17, 18, 20, 22-25, 36, 37 and 39-45 stand rejected and claims 46 and 47 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over to Aggarwal (U.S. Patent No. 5,672,347; issued 30 September 1997, Citation A on PTO-892 dated 15 April 2009), in view of Loetscher et al. (J. Biol Chem 1993, Citation U on PTO-892 dated 26 September 2007).

The Aggarwal patent discloses methods of treating autoimmune or inflammatory disorders (which are TNFSF meditated diseases) comprising administration of therapeutically effective amounts of an antagonist for TNF and teaches pharmaceutical compositions thereof, as in claim 45. The patent describes the function of the antagonists as either binding to or sequestering the TNF molecule itself with sufficient affinity and specificity to substantially neutralize the TNF epitopes responsible for TNF receptor binding or to compete with native TNF for the cell surface receptor or intracellular site to which TNF binds in the course of cell lysis (col.4, lines 48-65).

Examples include TNF antagonistic variants, which include substitutions, deletions or insertions of residues (amino acid sequence variants). Antagonistic TNF amino acid sequence variants are described as variants of the mature TNF amino acid sequence that are capable of inhibiting TNF cytotoxic activity, but which have substantially no cytotoxic activity of their own (col.5, lines 7-23). The difference between the disclosure of the Aggarwal patent and the claimed invention is that the patent does not teach the specific TNF substitutional variants of the instant claims.

However, upon reading the disclosure of the Aggarwal patent, the skilled artisan would have recognized the desirability of developing improved TNF substitutional variants for the treatment of TNF mediated diseases, i.e. autoimmune disorders or inflammatory disorders. Furthermore, Loetscher teaches mutated human TNF monomer proteins, which were analyzed for selective binding to recombinant p55 and p75 TNF receptors in competition with radiolabeled wild-type TNF. The reference teaches that mutations in the loop from position 29 to 34 (as in claim 43) and at positions 86 and 146 preferentially impaired binding to the 75-kDa TNF receptor, whereas mutations in the region from 143 to 145 mainly affected binding to the 55-kDa TNF receptor (abstract). The reference teaches mutants with substitutions at residues 65-76 (p.26352, col.2, third paragraph under Results), as in claim 40. The reference teaches that the substitutions are at receptor contact positions (p.26351, col.1), as in claim 23, and teaches surface substitutions (p.26352, col.1, first paragraph under Results), as in claim 37. In addition, the reference teaches non-conservative substitutions (e.g., p.26353, Table 1), as in claim 36. The reference teaches that selectivity for one or the other

receptor type was enhanced by combining two or three point mutations, the effects of the single mutations with respect to receptor selectivity being at least additive (abstract). Loetscher teaches that the mutants assembled into trimers, i.e. oligomers (p.26352, col.2, fourth paragraph under Results). The reference teaches that mutation of the conserved tyrosine 87 (Y87) amino acid residue resulted in a dramatic loss of binding activity to both TNF receptors (abstract, p.26352, second paragraph under Results, Table III on p.26355 and paragraph spanning pp.26355-26356). Mutants comprising the mutation A145R exhibited a complete loss of binding to the p55 TNF receptor and a 5-10 fold decrease in binding to the p75 TNF receptor and demonstrated no cytotoxic effects in a TNF cell cytotoxicity assay, even when present at high concentrations (p.26356, col.2, second paragraph). Loetscher does not explicitly disclose a TNF variant protein or mixes oligomer thereof that is substantially incapable of activation receptor signaling in all cognate receptors (both p55 and p75 receptors), with at least one substitution in the Large domain and at least one substitution in either the DE loop or the Small domain, as claimed.

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to modify the compositions and methods of Aggarwal as taught by Loetscher to yield predictable results. As evidenced by the Aggarwal patent, the skilled artisan would have known that developing TNF variant antagonists for methods of treating TNFSF mediated diseases, i.e. inflammatory or autoimmune disorders, would be desirable. The patent specifically guides the artisan to treat with TNF substitutional variants that are antagonistic to TNF receptors and are capable of

inhibiting TNF cytotoxic activity, but which have substantially no cytotoxic activity of their own. As evidenced by the Loetscher reference, the skilled artisan would have known that TNF substitutional variants comprising mutations at tyrosine 87 are not capable of binding to both TNF receptors and that mutants comprising the substitution A145R exhibit decreased binding to both receptors and exhibit no cytotoxicity (and would thus be useful as antagonists described by Aggarwal). A TNF variant monomer comprising both of these substitutions would meet all of the limitations of claims 17, 18, 20, 22-25, 36, 37, 39, 41, 42, 44, 46 and 47. As evidenced by both references, administration of the TNF variant monomer proteins for treatment of TNF-related disease would result in the formation of TNF mixed oligomers that are inactive bi-products of the treatment methods. Thus, it would have been reasonable to predict that the treatment methods of Aggarwal could be successfully practiced with TNF antagonistic protein variants that comprise substitutions taught by Loetscher. Given that Loetscher et al. teach the effect of combining single mutations would be additive and teach substitutions at positions that would abolish binding to either or both cognate receptors, which would be desirable for Aggarwal's methods, the skilled artisan would have found it obvious to generate a TNF mutant comprising the claimed substations for use in Aggarwal's methods. This is because the artisan has good reason to pursue the known options within his or her technical grasp to obtain predictable results. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. The motivation to arrive at the claimed invention flows naturally from the disclosure of the prior art references.

In the reply filed on 15 October 2009, applicants assert that applicants assert that Aggarwal discloses antagonistic TNF antibodies and discusses, in general, other potential TNF antagonists but provides no teaching or suggestion of TNF variants claimed. Applicants assert that Loetscher discloses variants that alter TNF receptor specificity but there is no teaching or suggestion of the claimed variants. Applicants assert that one of skill in the art would not have used the Y87 variant or A145R variant of Loetscher in a method to develop an antagonist as described in Aggarwal. Applicants assert that in column 5, lines 10-15 of Aggarwal, "Antagonistic TNF sequence variants will competitively bind to cell surface receptors ...thereby displacing TNF or preventing TNF from binding to or interacting with the cells." Applicants assert that the 87 variants "are not capable of binding to both TNF receptors" and the A145R variants exhibit decreased binging to both receptors". Thus, applicants assert that the skilled artisan would not view these as variants upon which to base a competitively binding antagonist as Aggarwal suggested. Applicants assert that neither reference discloses a mixed TNF oligomer, as in claim 17. Applicants assert that to modify Aggarwal with the variants with the teachings of Loetscher would render Aggarwal unsatisfactory for its intended purpose because the variants referenced by the Examiner do not meet the antagonist requirements posed in Aggarwal.

Applicants' arguments have been fully considered and are not found persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ

871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The Aggarwal patent discloses methods of treating autoimmune or inflammatory disorders (which are TNFSF meditated diseases) comprising administration of therapeutically effective amounts of an antagonist for TNF, and teaches that examples include TNF antagonistic variants with substitutions, deletions or insertions of residues. Further, Aggarwal's disclosure is not limited to those receptors that bind to TNF receptors, as applicants assert. The patent also describes the function of the antagonists as binding to or sequestering the TNF molecule itself with sufficient affinity and specificity to substantially neutralize the TNF epitopes responsible for TNF receptor binding (col.3, lines 48-65). Thus, the patent provides motivation to select for improved TNF substitutional variants for the treatment of TNF mediated diseases. The Loetscher reference teaches and suggests examples of such variants, since it teaches that TNF substitutional variants comprising mutations at tyrosine 87 are not capable of binding to both TNF receptors and mutants comprising the substitution A145R exhibit decreased binding to both receptors and exhibit no cytotoxicity. Moreover Loetscher teaches that the variant proteins still assembled into trimers (p.26352, col.2, 2nd full paragraph), thus suggesting the mixed oligomers of claims 17 and 23. Because of these properties, Loetscher's variants are suggested to be useful as antagonists described by Aggarwal.

Regarding applicants' assertion that the prior art references fail to disclose the specific variant set forth in the claims, specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involve not only what references expressly teach, but

what they would collectively suggest to one of ordinary skill in the art. See *CTS Corp. v. Electro Materials Corp. of America* 202 USPQ 22 (DC SNY 1979); and *In re Burckel* 201 USPQ 67 (CCPA 1979). As set forth above, specific variants of the claims are suggested by the Loetscher reference, i.e. comprising Y87 mutations and A145R, and Loetscher provides motivation to generate substitutional variants with more than one mutation. Given that Loetscher et al. teach the effect of combining single mutations would be additive, the artisan of ordinary skill would have found it *prima facie* obvious to generate a TNF mutant comprising these substitutions for use in Aggarwal's methods.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.
/G.E./

Gregory S. Emch
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Art Unit 1649
05 June 2010

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Primary Examiner, Art Unit 1649
June 6, 2010